Neurofibromatosis and hyperparathyroidism—A new syndrome?

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Co-existing tumours of endodermal and neuroectodermal origin have been reported frequently in recent years. Pheochromocytoma, parathyroid adenoma and thyroid carcinoma are the tumours usually involved.[1, 2] Recently we have observed two patients in whom hyperparathyroidism and neurofibromatosis occurred together. A search of the literature revealed that this association has been reported only once before, in the German literature.[3]

Case reports

Case 1

Mr. W.S., a 59-year-old bachelor, had had skin nodules and "café au lait" spots for as long as he could remember. A number of these nodules had been removed throughout the years and all were neurofibromata. In 1966 he began to complain of pain in his right foot. A radiograph at that time revealed decreased bone density and resorption of the tufts of terminal phalanges. On the basis of this finding, serum calcium and phosphorus were determined and were 12.5 mg. and 1.8 mg. per 100 ml. respectively. These tests were repeated several times in the outpatient department and the results were always abnormal, but it was not until October 1968 that the patient could be persuaded to enter hospital for investigation.

On admission his only complaint was back pain of many years' duration. Over the past 25 years he had fractured his left forearm three times, on each occasion owing to trauma, but denied any bone pain.

He was an only child, brought up in Russia. He claimed that neither of his parents had had any stigmata of neurofibromatosis, but said that his mother died of "sarcoma of the face" at the age of 40.

Examination revealed a small man of lively disposition. His skin was covered with a myriad of pink nodules (1 mm. to 3 cm. in diameter) and "café au lait" spots (Fig. 1). There was clubbing of the fingers, but the remainder of the physical examination was normal.

Results of biochemical investigation are summarized in Table I. Skeletal survey and intravenous pyelograms were normal. A trephine iliac crest biopsy showed osteitis fibrosa.

On the basis of these data an exploratory operation was carried out in November 1968 and a parathyroid adenoma was removed from the upper pole of the right thyroid lobe. Three other parathyroids were identified and found to be of normal appearance.

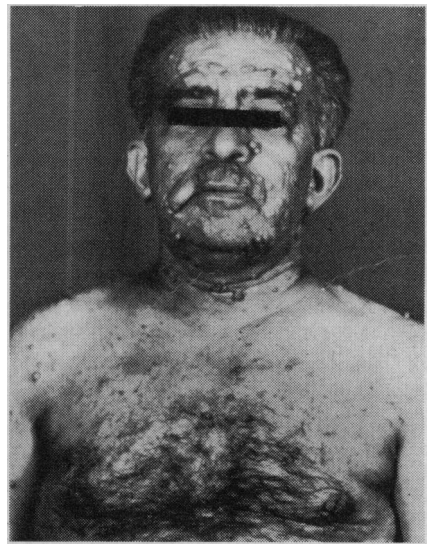

FIG. 1—Photograph of patient showing multiple skin nodules.

Postoperatively the patient became mildly hypocalcemic, but by the time of discharge the serum calcium had returned to normal. Follow-up serum calcium at six months was 9.4 mg. per 100 ml.

Case 2

This 34-year-old woman, a Greek immigrant, was brought to our attention by the Dentistry Department of McGill University because of recurrent, multiple giant cell reparative granulomata (epulis). In 1966 she had had an epulis removed and at that time serum calcium and skeletal survey were normal. In April 1968 she began to notice a midline swelling on the lingual aspect of her mandible which grew in size until October, when she again consulted the dentist. Biopsies revealed an epulis. The serum calcium on two occasions was 11.0 and 10.7 mg. respectively. She was admitted to the medical ward of the Montreal General Hospital in January 1969 to confirm the suspicion of hyperparathyroidism. On admission the patient complained only of a large painless mass in her lower jaw which bled easily and hindered her eating. She denied weight loss, anorexia or constipation. She did claim to be drinking more fluids than usual and had nocturia of recent onset.

There was no family history of neurofibromatosis.

The patient was a quiet, depressed, thin woman, who spoke only Greek. Examination of the eyes revealed dot-like opacities in the cortex of the lens. The lower jaw was protuberant and the mouth edentulous with a large (5 cm. x 3 cm.), bluish, friable mass replacing most of the lower gum and displacing the tongue upward and posteriorly. Several similar but much smaller lesions were seen on the upper gum.

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TABLE I
Pertinent preoperative laboratory values

	Normal range	*Case 1*	*Case 2*
Total calcium (mg.%)	9-11	11.9	11.5
Ionized calcium (mg.%)	4.5-6.4	5.95	5.75
Serum phosphorus (mg.%)	2.5-4.5	2.3	2.3
Alkaline phosphatase (K.-A. units)	3-13	8.8	14.0
Tubular reabsorption phosphorus	>85%	81%	82%
Urinary hydroxyproline (mg. per g. creatinine) on low gelatin diet	<25	43.0	109.0
Creatinine clearance (ml./min.)	100	104.8	101.0
Urinary calcium (mg./day) on 150 mg. calcium intake	<150	376	205

Multiple "café au lait" spots were noted over the skin, many of them greater than 1.5 cm. in diameter. Many subcutaneous nodules (1 to 3 mm. in diameter) were present, distributed randomly over the body; they were painless and a few were pedunculated.

The remainder of the physical examination did not disclose any abnormality.

The diagnosis of neurofibromatosis was established by biopsy.

The pertinent laboratory data are summarized in Table I. Skeletal survey and intravenous pyelograms were normal. The bone marrow was reported as showing iron deficiency. An iliac crest trephine biopsy was suggestive but not diagnostic of osteitis fibrosa.

Exploration of the neck was carried out in March 1969 and a 1.5-g. parathyroid adenoma was found at the inferior pole of the right lobe of the thyroid. Three other normal parathyroids were identified. A 1-cm. nodule was removed from the left lobe of the thyroid but was reported as normal thyroid tissue. The serum calcium fell to 7.0 mg. per 100 ml. two days after the operation and the patient was treated with calcium supplement and vitamin D, 50,000 units daily. Serum calcium had risen to 10.6 mg. at the time of discharge, and the vitamin D was discontinued in July. In August 1969 serum calcium was 10.0 mg.

Discussion

Neurofibromatosis has been linked with other tumours of neuroectodermal origin, such as pheochromocytoma, astrocytoma, schwannoma, intracranial hemangioma and many others.[4-8] These have been grouped together as the "neurocutaneous syndromes". Sipple[9] in 1961 showed that pheochromocytoma and carcinoma of the thyroid gland were also related, which suggests an association between tumours of the neurectoderm and tumours of the endoderm. In 1963 this was carried one step further by Manning *et al.*,[1] who reported a case of pheochromocytoma, hyperparathyroidism and thyroid carcinoma. Since then other reports have appeared.[10, 11] In 1966 Ruppert, Buerger and Chang[12] described a case of pheochromocytoma, neurofibromatosis and thyroid carcinoma. Our two cases presented parathyroid adenomata and neurofibromata, once again linking tumours of different cell origin.

The incidence of neurofibromatosis is approximately 1:3100 new admissions to hospital.[13] The incidence of hyperparathyroidism is less well known, but one study places it at 1:12,000 hospital admissions.[14] The fact that we saw two cases of neurofibromatosis associated with hyperparathyroidism in six months suggests that this may not be a coincidence. Because Sipple[9] drew attention to the increased incidence of carcinoma of the thyroid in patients with pheochromocytoma, the combination of the two diseases has been called Sipple's syndrome, and recently hyperparathyroidism has been added to this complex.[1] Although this syndrome involves multiple endocrine organs, it is differentiated from the condition of multiple endocrine adenomata (MEA) by the fact that pheochromocytoma arises from neurectodermal tissue and as such is never involved in the MEA syndrome. Our cases resembled Sipple's syndrome in that they combined parathyroid adenoma and tumour of the neurectoderm (neurofibroma). We would like to suggest that these tumours are genetically linked and that a whole spectrum of diseases exists which encompasses tumours of the neurectoderm, thyroid and parathyroid. If this is so, then patients with neurofibromatosis should be routinely screened for hyperparathyroidism and the other associated diseases. Long-term follow-up of all of these cases could be rewarded with an early diagnosis of the associated conditions.

Résumé

Neurofibromatose et hyperparathyroïdie

On note des cas où la neurofibromatose (maladie cutanée de von Recklinghausen) coexiste avec d'autres affections endocriniennes, dont la plus connue est le phéochromocytome. De même, on a déjà présenté des cas où l'hyperparathyroïdie primaire (maladie osseuse de von Recklinghausen) était associée à de l'adénomatose d'autres organes glandulaires. Nous avons récemment eu l'occasion d'observer l'apparition d'une hyperparathyroïdie primaire chez deux malades souffrant de neurofibromatose multiple. Dans chacun de ces cas, on retrouvait les caractéristiques diagnostiques de la maladie. Dans chaque cas également, on a constaté la présence d'un adénome parathyroïdien solitaire qui a été excisé. Durant la période postopératoire, les anomalies biochimiques ont été normalisées. Une revue de la littérature pertinente, dont celle concernant les travaux de Medlars, a permis de mettre à jour un cas semblable de cette association dans la littérature allemande. On conseille donc de procéder systématiquement à la recherche de signes d'hyperparathyroïdie chez des malades souffrant de neurofibromatose multiple.

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